Background Local bone destruction in rheumatoid arthritis, psoriasis arthritis or ankylosing spondylitis is a serious health burden and the major cause of disability and severely reduced quality of life in these diseases. This damage to the bony structures is exclusively mediated by a special cell type, the osteoclast (OC). Therefore, it is important to understand factors and pathways regulating the generation of OCs under inflammatory conditions. As PTEN is a lipid phosphatase and one of the main antagonists of the PI3-kinase pathway, we aimed to analyse the impact of the PI3-Kinase/PTEN axis on OC generation and bone biology in an animal model of inflammatory bone loss.

Methods We induced osteoclastogenesis in wt and PTEN deficient bone marrow cells and measured the generation of OCs, their resorptive capacity and induction of OC differentiation markers in vitro. Moreover, we analysed mice with a monocyte/macrophage-specific deletion of PTEN (myeloid specific PTEN-/-) by bone histomorphometry and crossed these mice into hTNFtg animals.

Results We show that myeloid specific PTEN-/- mice have increased osteoclastogenesis in vitro and in vivo when compared to wild-type animals. However, under non-inflammatory conditions, enhanced osteoclastogenesis did not result in systemic bone loss in vivo. However, when we crossed myeloid specific PTEN-/- into hTNFtg mice we found significantly decreased grip strength scores in myeloid specific PTEN-/-/hTNFtg mice compared to wt hTNFtg mice. Joint swelling scores, however, were not different between both groups. In line, myeloid specific PTEN-/-/hTNFtg mice displayed enhanced local bone destruction as well as OC formation in the inflamed joints, whereas the extent of synovial inflammation was not different between the groups. Analysis of the synovial membranes of wt and myeloid specific PTEN-/- animals revealed similar relative compositions of the cellular infiltrate including macrophages, which serve as OC precursors. This suggests that increased capacity for osteoclastogenic differentiation rather than enhanced recruitment of precursor cells is responsible for the enhanced local generation of OCs.

Conclusions Taken together, these data demonstrate that sustained PI3-Kinase activity in myeloid cells specifically elevated the osteoclastogenic potential of these cells, leading to enhanced inflammatory local bone destruction. Therefore, targeting the PI3-Kinase pathway therapeutically may be especially useful for the prevention of structural joint damage.

Background Our previous studies in the (NZBxNZW) F1 model provide strong rationales for an IL-2 based immunotherapy of lupus in order to restore regulatory T cell (Treg) mediated tolerance that is impaired due to an acquired IL-2 deficiency (Humrich et al., 2010). However, because of its pleiotropy, other cells than Treg can be activated by IL-2 in a dose dependent manner, which may induce unwanted side effects or even trigger autoimmunity.

Objectives To determine an optimal regimen for an IL-2 based immunotherapy that is capable to induce a sufficient expansion of CD4+Foxp3+ Treg in vivo while only marginally affecting other cells, and that most efficiently influences active disease in the (NZBxNZW) F1 model for lupus.

Methods Recombinant mouse IL-2 at various single doses was injected subcutaneously either into young or diseased (NZBxNZW) F1 mice every 4 days until the end of the experiment. Control animals received an equal amount of PBS (carrier). Cells from lymphoid organs and peripheral blood were analysed by flow cytometry at different time points throughout the study. In addition survival and clinical parameters (weight, proteinuria, leukozyturya, autoantibodies) were analysed during IL-2 therapy of diseased mice for regimens with the single dosages of 5 ng/g and 25 ng/g body weight.

Results We found that the low-dose IL-2 regimen with a single dose of 5 ng/g body weight sufficiently promoted the expansion of CD4+Foxp3+Treg, while not or only marginally affecting CD4+ conventional T cells (Tcon) and other potentially harmful cells. Although higher doses of IL-2 resulted in a more pronounced proliferation and expansion of Treg, this was accompanied by a considerable increase in CD4+ memory/effector Tcon and NK/NKT cells. Clinically, regimens with both 5 ng/g and 25 ng/g were almost equally sufficient to influence nephritis and to decrease mortality in mice with established disease.

Conclusions These studies show that a low-dose IL-2 regimen selectively targets Treg and is clinically effective and also safe in murine lupus providing essential rationales for the clinical introduction of an IL-2 based immunotherapy in SLE.

References
A9.8 Low-Dose IL-2 Therapy Selectively Expands Regulatory T Cells and Ameliorates Established Disease in (NZBxNZW) F1 Lupus Mice

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Ann Rheum Dis 2013 72: A67
doi: 10.1136/annrheumdis-2013-203223.8

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